

Title: Investigations of Viral Carcinogenesis in Primates

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Objectives: (1) Evaluation of long-term oncogenic effects of human and animal viral inocula in primates of various species, especially newborn macaques; (2) maintenance of monkey breeding colonies and laboratories necessary for inoculation, care and monitoring of monkeys; and (3) biochemical studies of transfer RNA under conditions of neoplastic transformation and studies on the significance of RNA-dependent DNA polymerase in human leukemic tissues.

Major Findings: This contractor continues to produce over 300 excellent newborn monkeys per year. This is made possible by diligent attention to reproductive physiological states of female and male breeders. Semen evaluation, artificial insemination, vaginal cytology and ovulatory drugs are used or tried as needed.

Inoculated and control infants are hand-fed and kept in modified germ-free isolators. They are removed from isolators at about 8 weeks of age and placed in filtered air cages for months or years of observation. The holding area now contains approximately 1200 animals up to 5 years old. Approximately 300 are culled every year at a rate of about 25 per month. This is necessary to make room for young animals inoculated with new or improved virus preparations.

During the past year macaques were inoculated at birth or in utero with the Mason-Pfizer monkey mammary virus, Epstein-Barr virus, Herpesvirus saimiri, and Marek's disease virus. EB virus was given with immunostimulation and immunosuppression (ALS, prednisone, imuran). Australia antigen was given to newborn African green monkeys.

The breeding and holding colonies were surveyed for antibody to EBV. All breeders were positive and their offspring contain maternal antibody for several months. Colony-born offspring that have lost maternal antibody and are sero-negative will be surveyed periodically for conversion to the EB positive state.

An RNA-dependent DNA polymerase similar to that associated with RNA tumor viruses was detected in human leukemic cells but not in normal cells stimulated by phytohemagglutinin. The enzyme was isolated, purified and concentrated 200-fold, making possible its further characterization and study in relation to the leukemic process in man.

Significance to Biomedical Research and to the Program of the Institute: Inasmuch as tests for the biological activity of candidate human viruses will not be tested in the human species, it is imperative that another system be developed for these determinations and, subsequently for the evaluation of vaccines or other measures of control. The close phylogenetic relationship of the lower primates to man justifies utilization of these animals for these purposes. Further study of altered transfer RNA and polymerase enzymes would determine their significance in neoplastic change and provide a basis for selection of therapeutic agents.

Proposed Course: Continuation with increased emphasis on monitoring and intensive care of inoculated animals to determine if active infection occurs, effects of infection, and degree of immunosuppression when used. Further studies of human neoplasms at a molecular level will continue.

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